

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203756Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Risk Management Review**

Date: November 1, 2012

Reviewer(s): Joyce Weaver, Pharm.D., Risk Management Analyst  
Division of Risk Management (DRISK)

Team Leader: Cynthia LaCivita, Pharm.D., DRISK

Division Director: Claudia Manzo, Pharm.D., DRISK

Drug Name(s): Cometriq (cabozantinib)

Therapeutic Class: Tyrosine kinase inhibitor antineoplastic

Dosage and Route: 140mg orally once daily

Application Type/Number: NDA 203756

Submission Number: Application filed May 29, 2012

Applicant/sponsor: Exelixis Inc

OSE RCM #: 2012-1310

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## **1 INTRODUCTION**

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is needed for cabozantinib.

Exelixis, Inc filed an application for Cometriq (cabozantinib) for the treatment of patients with progressive, unresectable, locally advanced or metastatic medullary thyroid cancer (MTC). In the pivotal clinical trial, patients who received Cometriq had significantly longer progression-free survival (PFS) and significantly higher overall response rate (ORR).

Serious safety issues for Cometriq include hemorrhage, gastrointestinal (GI) and non-GI perforations and fistulas (a boxed warning is proposed for these events), thrombotic events, wound complications, hypertension, osteonecrosis of the jaw, reversible posterior leukoencephalopathy syndrome (RPLS), palmar-plantar erythrodysesthesia (PPE) syndrome, proteinuria, drug interactions, hepatic impairment, and embryo-fetal toxicity. QT prolongation is not a serious safety concern for Cometriq.

The sponsor did not propose a REMS or a risk management plan (RMP).

## **2 BACKGROUND**

Cometriq (cabozantinib) is under consideration for the treatment of patients with progressive, unresectable, locally advanced or metastatic medullary thyroid cancer (MTC). The proposed dose is 140mg daily, by mouth. Caprelsa (vandetanib), a drug in the same drug class as Cometriq, was approved with a REMS to mitigate the risk of QT prolongation.

Cometriq was studied in a randomized, placebo-controlled Phase 3 trial in 330 patients. The patients were randomized 2:1 to receive cabozantinib or placebo. The primary endpoint was PFS. Overall survival (OS) and ORR were secondary endpoints. For the primary endpoint, there was a significant better PFS in the treatment group compared to the placebo group. The ORR was significantly better in the treatment group.

Adverse events occurred in 100% of the cabozantinib-treated patients and 95% of the patients receiving placebo. Grade 3-4 adverse events were observed in 76% of patients who received cabozantinib; this was twice the rate of grade 3-4 events in the placebo arm. The most frequently seen grade 3-4 events were diarrhea (16%), PPE syndrome (13%), fatigue (9%), and hypertension (8%).

## **3 REGULATORY HISTORY**

Exelixis, Inc opened an investigational new drug (IND) program for cabozantinib in July 2005. In June 2008, the sponsor and the Agency reached agreement on a Special Protocol Assessment (SPA) to study cabozantinib for the purposes of submitting a new drug application (NDA) to the Agency. In March 2008, the Agency agreed that PFS may be an acceptable endpoint in the trial. Orphan drug designation was granted November 2010. A pre-NDA meeting was held December 2010. In April 2011, fast track designation was granted for unresectable, locally advanced, or metastatic MTC. The initial module of the rolling NDA submission was received December 2011, and the final module, the clinical

module was received in May 2012. According to the timeframes outlined in the Prescription Drug User Fee Act (PDUFA), action should be taken by the Agency on the application by November 29, 2012.

### **3.1 PRODUCT LABELING**

The FDA-edited proposed labeling includes the following adverse reactions in the Warnings and Precautions section of the labeling.

- Gastrointestinal (GI) and non-GI perforations and fistulas
- Hemorrhage
- Thrombotic events
- Wound complications
- Hypertension
- Osteonecrosis of the jaw
- PPE syndrome
- Proteinuria
- RPLS
- Drug interactions
- Hepatic impairment
- Embryo-fetal toxicity

The clinical reviewer has proposed placing hemorrhage, GI and non-GI perforations and fistulas into a boxed warning.

A description of a concentration-dependent increase in the QT interval is proposed for the Clinical Pharmacology section of the labeling. QT prolongation is not included in the FDA-edited Warnings and Precautions section of the labeling.

## **4 MATERIALS REVIEWED**

### **4.1 DATA AND INFORMATION SOURCES**

We reviewed the following materials from the May 29, 2012 NDA submission:

- Proposed labeling
- Dear Healthcare Provider letter
- Dear Professional Organization letter

We reviewed the following additional materials, generated during the Agency review of the NDA:

- Clinical safety analysis presented at the August 28, 2012 midcycle meeting
- Efficacy analysis presented at the August 28, 2012 midcycle meeting

- Interdisciplinary Review Team for QT Studies Consultation: QT Study Review, October 31, 2012
- FDA edited product labeling

## **5 RESULTS OF REVIEW**

### **5.1 OVERVIEW OF CLINICAL PROGRAM**

Cometriq (cabozantinib) was studied in a randomized, placebo-controlled Phase 3 trial in 330 patients. The patients were randomized 2:1 to receive cabozantinib or placebo. The primary endpoint was PFS. Overall survival (OS) and ORR were secondary endpoints. For the primary endpoint, there was a significant ( $p < 0.0001$ ) PFS of 11.2 months, compared to 4 months in the placebo group. The ORR was significantly ( $p < 0.0001$ ) better in the treatment group. The OS data had not matured at the time of submission.

In addition to the 214 patients exposed to cabozantinib in the pivotal trial, two additional trials, a Phase 1 trial and a Phase 2 trial, with exposure to 81 additional patients contributed to the safety database.

### **5.2 SAFETY CONCERNS**

#### **Grade 3-4 Adverse Events**

Adverse events occurred in 100% of the cabozantinib-treated patients and 95% of the patients receiving placebo. Grade 3-4 adverse events were observed in 76% of patients who received cabozantinib; this was twice the rate of grade 3-4 events in the placebo arm. The most frequently seen grade 3-4 events were diarrhea (16%), PPE syndrome (13%), fatigue (9%), and hypertension (8%).

Toxicities known to occur with this drug class that were observed in the cabozantinib trials include hypertension, hemorrhage, venous and arterial thrombosis, GI and non-GI fistulas, GI perforations, proteinuria, wound complications, osteonecrosis, and RPLS. Fatalities occurred with hemorrhage and GI and non-GI fistulas, but the contribution of the drug vs. the contribution of the patient's underlying disease was not clear in the fatal cases. In the judgment of the clinical reviewer, the toxicities of cabozantinib are manageable, and, with the exception of PPE syndrome, were similar to those observed with vandetanib, an antineoplastic of the same class. Palmar-plantar erythrodysesthesia syndrome occurred in 13% of patients receiving cabozantinib; this event is not common with vandetanib.

#### **QT Prolongation**

Vandetanib has a risk evaluation and mitigation strategy (REMS) to mitigate the risk of QT prolongation. The REMS requires that prescribers be certified. In clinical testing, vandetanib caused mean increases of QTcF of 35 ms, and increases in excess of 60 ms in 36% of patients receiving the usual dose of 300mg once daily. Additionally, 4.3% of patients receiving vandetanib had QTcF > 500 ms. Cases of torsades de pointes, ventricular tachycardia, and sudden death have occurred with vandetanib.

Patients receiving cabozantinib had increases of QTcF of 10-15 ms. No cases of torsades de pointes was observed in the clinical testing program, and no patient had QTcF>500 ms. One patient experienced a QTcB of >500 ms with cabozantinib.

Two patients in the clinical trial died possibly secondary to sudden death. One patient, a 67-year-old man, had measured QTcF ranging from 392 to 415 ms. The second patient, a 58-year-old man, had measured QTcF ranging from 407 to 427 ms. Neither patient had EKGs with QRS morphology suggestive of torsades de pointes. EKGs were not available of the terminal event. A contribution of cabozantinib to sudden death cannot be ruled out for these two events.

The CDER Interdisciplinary Review Team for QT Studies reviewed the QT data submitted with the application. The review supported a finding that there is likely a small dose-related increase in the QT interval with cabozantinib. The review supports the sponsor's proposed product labeling regarding the magnitude of the increase in QTcF with cabozantinib.

### **Embryo-fetal toxicity**

Based on pre-clinical studies and the mechanism of action of cabozantinib, it is assumed that cabozantinib can cause fetal harm. In pre-clinical studies, cabozantinib was embryolethal in rats at exposures below the recommended human dose. There were increased incidences of cardiovascular and skeletal malformations in rats, and visceral variations and malformations in rabbits. The proposed labeling advises that females of reproductive potential should use effective contraception, and should avoid becoming pregnant for at least four months after their last dose of cabozantinib. This advice is presented to patients in the proposed Medication Guide. The same advice is presented in the Caprelsa (vandetanib) label. The REMS for Caprelsa does not address the risk of teratogenicity.

## **5.3 APPLICANT'S PROPOSAL FOR RISK MANAGEMENT**

The applicant did not propose a REMS or RMP for cabozantinib. However, the applicant submitted proposed Dear Healthcare Provider and Dear Professional Society letters informing healthcare providers of the safety concerns detailed in the Warnings and Precautions section of the proposed labeling including GI perforations, GI and non-GI fistulas and abscesses, thrombotic events and hemorrhage, wound complications, hypertension, osteonecrosis, RPLS, an increase in QTcF of 10-15 ms, and hazard to the developing fetus.

### **5.3.1 Proposed Postmarketing Studies**

The clinical reviewer has proposed the following safety-related postmarketing requirements:

Submission of the final OS analysis

- A study to assess safety/efficacy of a lower treatment dose of cabozantinib
- A study to assess safety in patients with mutations in the RET proto-oncogene
- A study to assess safety in patients with renal function impairment

## 6 DISCUSSION

### Consideration of REMS under FDAAA

The Food and Drug Administration Amendments Act (FDAAA) of 2007 requires that the Agency consider six factors in determining whether a REMS is needed for a given product. These factors are: the estimated size of the population likely to use the drug involved, the seriousness of the disease or condition that is to be treated with the drug, the expected benefit of the drug with respect to such disease or condition, the expected or actual duration of treatment with the drug, the seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug, and whether the drug is a new molecular entity. After considering these factors, a REMS should be instituted for a product if the REMS is needed to ensure that the benefits of the product outweigh its risks.

The data for the six factors for Cometriq are detailed below.

- The estimated size of the population likely to use the drug involved.
  - The National Cancer Institute estimates that about 56,460 new cases of thyroid cancer will occur in the United States in 2012. Medullary thyroid cancer comprises 3% (1,694) to 4% (2,258) of all thyroid cancers. The overall survival of patients with MTC is 86% at 5 years and 65% at 10 years. Poor prognostic factors include advanced age, advanced stage, prior neck surgery, and associated multiple endocrine neoplasia.
- The seriousness of the disease or condition that is to be treated with the drug.
  - The National Cancer Institute estimates that 1,780 patients will die secondary to thyroid cancer in 2012. If the yearly deaths from thyroid cancer are in proportion to the incidence of the subtypes of thyroid cancer, this will represent 53 to 71 deaths from MTC.
- The expected benefit of the drug with respect to such disease or condition.
  - Patients treated with cabozantinib had improved PFS, the primary endpoint; there was a significant ( $p < 0.0001$ ) PFS of 11.2 months, compared to 4 months in the placebo group. The ORR was significantly ( $p < 0.0001$ ) better in the treatment group. The OS data had not matured at the time of submission.
- The expected or actual duration of treatment with the drug.
  - Patients are treated with Cometriq until disease progression or unacceptable toxicity occurs. The median duration of response in patients studied was 14.6 (95% CI, 11.1 to 17.5) months.
- The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.
  - The adverse events reported with cabozantinib are generally consistent with known adverse events with this class of antineoplastic. Grade 3-4

adverse events were observed in 76% of patients who received cabozantinib; this was twice the rate of grade 3-4 events in the placebo arm. The most frequently seen grade 3-4 events were diarrhea (16% in the treatment group compared to 1.8% in the control group), PPE syndrome (13% compared to 0%), fatigue (9% compared to 3%), and hypertension (8% compared to 0%).

- Whether the drug is a new molecular entity (NME).
  - Cometriq is an NME.

### **REMS Considerations**

The types of toxicity with cabozantinib appear to be similar to vandetanib, except that PPE syndrome occurred in 13% of patients receiving cabozantinib; this event is not common with vandetanib. QT prolongation occurs with both cabozantinib and vandetanib, but the magnitude of the prolongation is less with cabozantinib. According to the QT team's review of QT effects of cabozantinib, cabozantinib causes a small dose-related increase in QT. The review supported the language in the labeling regarding the magnitude of the increase in QT measured in clinical testing.

In the judgment of the clinical reviewer, the toxicities of cabozantinib are manageable, and, with the exception of PPE syndrome, were similar to those observed with vandetanib, an antineoplastic of the same class. Palmar-plantar erythrodysesthesia syndrome occurred in 13% of patients receiving cabozantinib; this event is not common with vandetanib. Palmar-plantar erythrodysesthesia occurs with numerous antineoplastic drugs. Oncologists are familiar with PPE and its management; this event can be managed with labeling.

## **7 CONCLUSION**

According to the clinical review, there is evidence of benefit for Cometriq based on the magnitude of the effect on PFS, the consistency of benefit in various subgroups, and consistency in secondary endpoints. The risk–benefit assessment for Cometriq supports approval.

We agree with the clinical reviewer that the toxicities of cabozantinib appear to be appropriate to be managed with labeling. We do not recommend a REMS for Cometriq at this time. Should Dear Healthcare Provider and Dear Professional Society letters be issued for Cometriq, we recommend that the letters be issued outside of a REMS.

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11/01/2012

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